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MANNICH REACTION IN A NUMBER OF SIX-MEMBERED HETEROCYCLIC γ-KETONES. X*. STEREOCHEMISTRY OF THE REDUCTION AND PHENYLATION OF 2,2-DIMETHYL-5-DIMETHYLAMINOMETHYL-4-OXOTETRAHYDROPYRAN

E. T. Golovin, B. M. Glukhov, and L. S. Botsman

USC 547.811:541.63:542.941.7:543.422.25.4'544

2,2-Dimethyl-5-dimethylaminomethyl-4-oxotetrahydropyran was subjected to reduction with lithium aluminum hydride, sodium borohydride, aluminum isopropoxide, and lithium in liquid ammonia, to catalytic hydrogenation over Raney nickel, and phenylation with phenyllithium. The quantitative ratios in the resulting mixtures of stereoisomeric 2,2-dimethyl-5-dimethylaminomethyl-4-hydroxytetrahydropyrans and their dependence on the character of the reducing agents were established by means of gas—liquid chromatography and PMR spectroscopy. The individual geometrical isomers of the amino alcohols were isolated, and their three-dimensional structures were studied by means of their PMR and IR spectra.

In addition to its theoretical interest, the investigation of the stereochemical principles of the reduction and phenylation of variously substituted β-amino ketones, readily obtained by Mannich reaction from six-membered heterocyclic γ-ketones, is of value for the development of stereospecific methods for the synthesis of esters of the corresponding secondary and tertiary γ-amino alcohols and clarification of the dependence of their physiological activities on their three-dimensional structures.

Up until now, we have studied the stereochemistry of the indicated reactions in the case of sterically unhindered cyclic amino ketones [2-4]. In the present communication we describe the reduction and phenylation of 2,2-dimethyl-5-dimethylaminomethyl-4-oxotetrahydropyran (I) [5], which contains two methyl groups in the meta position with respect to the carbonyl group, one of which is axially oriented. It is well known [6] that this sort of

*See [1] for communication IX.

M. V. Lomonosov Moscow Institute of Fine Chemical Technology. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 5, pp. 611-616, May, 1976. Original article submitted April 24, 1975.

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TABLE 1. Yields and Quantitative Ratios of the trans and cis Isomers of Amino Alcohols as a Function of the Reducing Agent

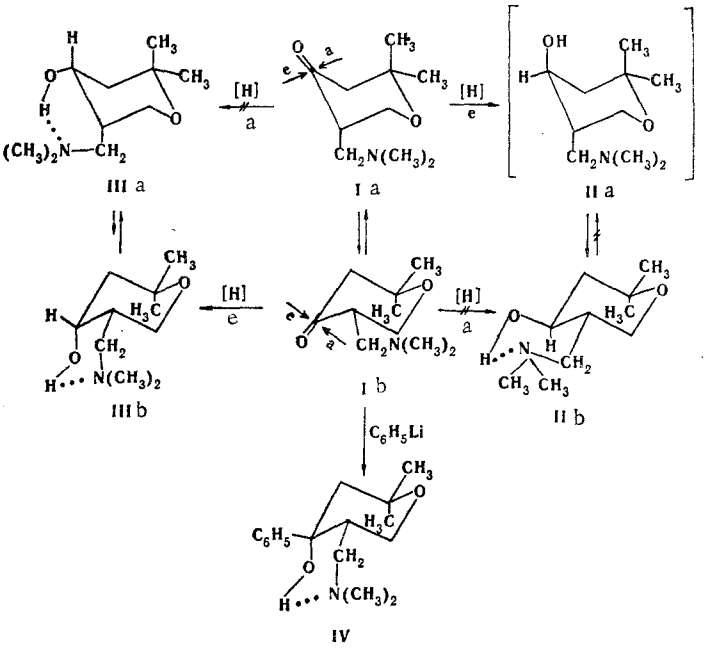
Reducing agent	Overall yield, %	Isomer content, %	
		trans	cis
Li/liquid NH_3	66	98	2
$LiAlH_4$ in ether	73	54	46
$NaBH_4$ in 1 *N* NaOH	62	35	65
Al (iso-$C_3H_7O)_3$ in iso-C_3H_7OH	50	41	59
H_2/Ni	80	51	49

substituent orientation creates steric hindrance in nucleophilic addition reaction involving the carbonyl group of the cyclic ketone and thereby introduces its peculiarities into the stereochemistry of these reactions. In this connection, it was of interest to ascertain the stereospecificity of the reduction and phenylation of hindered cyclic amino ketone I. A mixture of two geometrical isomers of secondary amino alcohols — trans-2,2-dimethyl-5e-dimethylaminomethyl-4e-hydroxy- (IIb) and cis-2,2-dimethyl-5a-dimethylaminomethyl-4e-hydroxytetrahydropyran (IIIa) (Table 1) — is formed in the reduction of I with lithium aluminum hydride, sodium borohydride, and aluminum isopropoxide, and also by hydrogenation over a Raney nickel catalyst.

Thus, whereas 54% of the trans amino alcohol II is present in the mixture formed by reduction with lithium aluminum hydride, a mixture with predominance of cis amino alcohol III is obtained by reduction with sodium borohydride and aluminum isopropoxide, and catalytic hydrogenation gives a mixture of almost equal amounts of the trans and cis isomers of amino alcohols II and III. The reaction proceeds stereospecifically to give practically only the trans amino alcohol of II only in the case of reduction with lithium in liquid ammonia. Both the amino ketone base I and its hydrochloride underwent reduction; in the case of the hydrochloride the reaction gives a mixture of stereoisomeric amino alcohols II and III in somewhat higher overall yields, but their ratio does not change substantially. We also noted this sort of regularity in [4]. The phenylation of amino ketone I with phenyllithium gives only one tertiary amino alcohol — 2,2-dimethyl-4e-phenyl-5e-dimethylaminomethyl-4a-hydroxytetrahydropyran (IV) — in 57% yield. The quantitative ratio of the isomers in the mixture was determined by gas—liquid chromatography (GLC) and PMR spectroscopy [7,8]. The possibility of the application of PMR spectroscopy for this purpose in this case was based on the fact that singlets of the protons of the axial methyl groups in the 2 position, the chemical shifts of which differ for amino alcohols II and III, can be identified in the PMR spectra of the mixture. The individual geometrical isomers of amino alcohols II and III were isolated by fractional crystallization of the mixtures of the bases and their hydrochloride salts. Their three-dimensional structures were established by means of their PMR and IR spectra [8,9]. Acylation of amino alcohols II-IV with acetyl chloride gave their acetates (V-VII) (see scheme on following page).

Intense absorption bands in the region of the stretching vibrations of a hydroxyl group linked a hydrogen bond with the nitrogen atom of an amino group (ν 3310, 3250, and 3160 cm^{-1}, respectively) are observed in the IR spectra of dilute solutions of amino alcohols II-IV. For the formation of an intramolecular hydrogen bond in cyclic γ-amino alcohols the vicinal aminomethyl and hydroxyl groups should be trans-diequatorially oriented or cis-equatorially—axially oriented relative to one another.

Multiplet signals of the 4-H proton, shifted to weak field because of deshielding by geminal hydroxy or acetoxy groups, are present in the PMR spectra of amino alcohol II and its acetate V at δ 3.64 and 4.64 ppm, respectively. The spin—spin coupling constants (SSCC) of this proton with the vicinal 3-H and 5-H protons (J_{4a3a} = 11 Hz, J_{4a3a} = 5 Hz, and J_{4a5a} = 11 Hz) constitute evidence for axial orientation of the 4- and 5-H protons and, consequently, for equatorial orientation of both the hydroxy (or acetoxy) and aminomethyl group adjacent to them. According to the PMR spectrum of amino alcohol III, the SSCC with the 3- and 5-H protons (J_{4a3a} = 11 Hz, J_{4a3e} = 5 Hz, and J_{4a5e} = 5 Hz) found from the multiplet signal of the



4-H proton (δ 3.92 ppm) correspond to one diaxial and two axial—equatorial interactions. Consequently, amino alcohol III, like amino alcohol II, is the equatorial isomer, but its aminomethyl group is axially oriented, inasmuch as the 4-H proton is axially oriented, and the 5-H proton is equatorially oriented. In addition, in the PMR spectra of amino alcohols II and III it was found to be possible to identify two resonance signals of axial and equatorial 6-H protons, the analysis of which confirms the above-expressed conclusions regarding the orientation of the proton and the aminomethyl group in the 5 position. Thus the PMR spectrum of amino alcohol II contains a triplet from the 6-H_a proton at δ 3.07 ppm (J_{6a5a} = 11 Hz, J_{6a6e} = -11 Hz) and a quartet from the 6-He proton at δ 3.48 ppm (J_{6e5a} = 5 Hz, J_{6e6a} = −11 Hz), whereas the PMR spectrum of amino alcohol III contains two quartets from the 6-H_a proton at δ 3.42 ppm and the 6-H_e proton at δ 3.58 ppm, the SSCC of which with the 5-H_e proton are 3 Hz (J_{6a6e} = −11 Hz) in both cases. Additional information regarding the orientation of the hydroxy group in amino alcohols II and III may be given by the IR spectra of their acetates (V and VI), in which the presence of a singlet absorption band of the stretching vibrations of the C—O bond at 1240 cm^{-1} indicates an equatorial orientation of the acetoxy group [2,4]. Thus, on the basis of the data obtained from the PMR and IR spectra, one may arrive at the conclusion that amino alcohol KK in solution has a preferred conformation with a trans-diequatorial orientation of the hydroxy and aminomethyl groups, whereas amino alcohol III has a cis configuration relative to these groups and a preferred conformation with an equatorial hydroxy and axial aminomethyl groups. Insofar as the three-dimensional structure of tertiary amino alcohol IV is concerned, the presence of a bulky phenyl substituent in the 4 position, which should preferably be equatorially oriented, and the presence in the IR spectrum of the strong absorption band of a hydroxy group included in an intramolecular OH...N hydrogen bond (3160 cm^{-1}) constitute evidence in favor of the existence of amino alcohol IV in a preferred conformation with axial hydroxy and equatorial aminomethyl groups [1]. This conclusion is also confirmed by the fact that the IR spectrum of its acetate (VII) contains a triplet absorption band of a C—O bond at 1240-1275 cm^{-1}, which is characteristic for an axial acetoxy group [2,4].

The three-dimensional structures and the quantitative ratio of stereoisomeric amino alcohols II and III in the mixtures formed in the reduction of amino ketone I by various reducing agents show that the reaction evidently takes place with the participation of conformers Ia and Ib, which exist in a state of conformational equilibrium in solution [1,5]. It is completely apparent that, as in the case of phenyllithium, when the hydride ion approaches the carbonyl group from the most accessible equatorial region, axial amino alcohols IIa, IIIb, and IV will be obtained. The approach of the reagents from the axial side is hindered by the axial methyl group in the 2 position. Evidence for the participation of the two conformers of amino ketone I in the reaction may also be had from the result of its catalytic

hydrogenation, in which axial alcohols are usually formed, inasmuch as adsorption of the ketone molecule on the catalyst surface and the approach of hydrogen take place on the unhindered equatorial side [6]. Because of its extreme steric and thermodynamic instability, amino alcohol IIa is then inverted to equatorial conformer IIb with realization of a OH...N hydrogen bond. Amino alcohol III is most likely a mixture of conformers IIIa and IIIb with a shift of the equilibrium to favor conformer IIIa. However, one cannot exlude the possibility of participation also of the flexible form of amino ketone I in the reduction [1], inasmuch as the difference in the energies of the chair form and the flexible form of substituted six-membered cyclic ketones is small [6]. In this case steric hindrance will be at a minimum because both of the methyl substituents in the 2 position are oriented symmetrically with respect to the ring and the probabilities of approach of the reducing agent to the carbonyl group from either side will be almost identical; this will also lead to the formation of a mixture of epimeric amino alcohols II and III.

EXPERIMENTAL

The PMR spectra of carbon tetrachloride solutions of II and III were obtained with a Varian HA-100 spectrometer with tetramethylsilane as the internal standard. The IR spectra of carbon tetrachloride solutions of amino alcohols II-IV ($5 \cdot 10^{-3}$ M) and thin layers or mineral oil suspensions of their acetates (V-VII) were recorded with a UR-10 spectrometer with an LiF prism. Analytical GLC was carried out with an LKhM-7A chromatograph with a catharometer detector and a 4 × 1000 mm stainless-steel column; the stationary phase was polyethylene glycol adipate on Celite, the carrier gas was helium, the flow rate was 30 ml/min, and the operating temperature was 170°. Thin-layer chromatography was carried out on plates with a loose layer of activity II aluminum oxide in a petroleum ether—ether system (1:4). The hydrochlorides were obtained by the addition of a saturated solution of dry hydrogen chloride in anhydrous ether to a solution of the base in ether. The salts were crystallized from alcohol—acetone (1:3), and the bases were crystallized from hexane.

Reduction of 2,2-Dimethyl-5-dimethylaminomethyl-4-oxotetrahydropyran (I). A) A solution of 11g (0.05 mole) of the hydrochloride of amino ketone I in 100 ml of alcohol was added with stirring and cooling (to −70°) to 300 ml of liquid ammonia, after which 2.8 g (0.4 g-atom) of fine lithium shavings was added in small portions. The cooling bath was removed, and the temperature of the reaction mixture was gradually raised to room temperature. The ammonia was evaporated completely, and the mixture was hydrolyzed with 150 ml of water. The mixture was saturated with potassium carbonate and extracted repeatedly with ether. The ether extracts were dried with $MgSO_4$, the ether was removed by distillation, and the residue was vacuum distilled to give 6.2 g (66%) of a substance with bp 105-107° (1), which crystallized on standing. According to the PMR spectral data, the reaction product consisted of 98% trans-amino alcohol II. Recrystallization gave a product with mp 54-56° and R_f 0.56. IR spectrum: 3310 cm^{-1} (OH_{bond}); the integral intensity was $6.02 \cdot 10^4$ $cm^{-2} \cdot mole^{-1} \cdot liter$. Found: C 63.9, 63.9; H 11.0, 11.2; N 7.6, 7.5%. $C_{10}H_{21}NO_2$. Calculated: C 64.1; H 11.3; N 7.5%. The hydrochloride had mp 224-225°. Found: Cl 15.7, 15.8%. $C_{10}H_{21}NO_2 \cdot HCl$. Calculated: Cl 16.0%.

B) An 11-g (0.05 mole) sample of the hydrochloride of amino ketone I was added in small portions with stirring and cooling (to −30°) to a suspension of 1.5 g (0.03 mole) of lithium aluminum hydride in 200 ml of anhydrous ether. The temperature was then gradually raised to room temperature, and the mixture was refluxed for 2 h. It was then cooled to −20° and hydrolyzed successively with 6 ml of water and 1.5 ml of 15% NaOH solution. The solid material was removed by filtration and washed on the filter with ether. The ether solution was dried with $MgSO_4$ and the ether was removed by vacuum distillation to give 6.8 g (73%) of a mixture of amino alcohols II and III with bp 70-76° (0.5 mm) and R_f 0.56 and 0.40. According to GLC, the mixture contained 54% amino alcohol II and 46% amino alcohol III (the retention times were 15.2 and 17.3 min, respectively). A 7.6-g sample of the mixture of hydrochlorides obtained from amino alcohols II and III was crystallized to give 2.2 g of the salt as individual trans amino alcohol II with mp 223-225°. Amino alcohol base II, which was isolated from the salt by treatment with an aqueous solution of potassium carbonate and extraction with ether, began to crystallize after removal of the ether by distillation to give a product with mp 54-56°.

Reduction of 9.3 g (0.05 mole) of amino ketone base I with 1 g (0.025 mole) of lithium aluminum hydride in 150 ml of ether gave 6.4 g (68%) of a mixture of amino alcohols II and III with the same composition as in the preceding experiment; the mixture had bp 72-77° (0.5 mm) and R_f 0.56 and 0.40.

C) An 11-g (0.05 mole) sample of the hydrochloride of amino ketone I was added with cooling (to 0°) to a solution of 1 g (0.025 mole) of sodium borohydride in 250 ml of 1 N NaOH solution, and the mixture was stirred at 20° until the reaction was complete (as monitored by GLC). It was then saturated with potassium carbonate, and the reduction product was extracted with ether. The extract was dried with $MgSO_4$ and vacuum distilled to give 5.8 g (62%) of a mixture of amino alcohols III and II with bp 74-78° (0.5 mm) and R_f 0.40 and 0.56; according to the PMR spectral data, the mixture contained 65% amino alcohol III and 35% amino alcohol II. Crystallization of the mixture gave 2 g of pure cis-amino alcohol base III with mp 34-35° and R_f 0.40. IR spectrum: 3250 cm^{-1} (OH_{bond}); the integral intensity was $4.42 \cdot 10^4$ $cm^{-2} \cdot mole^{-1} \cdot liter$. Found: C 64.1 64.2; H 11.3, 11.4; N 7.2, 7.1%. $C_{10}H_{21}NO_2$. Calculated: C 64.1; H 11.3; N 7.5%. The hydrochloride had mp 180-182°. Found: Cl 16.3, 16.2%. $C_{10}H_{21}NO_2 \cdot HCl$. Calculated: Cl 16.0%.

D) A mixture of 9.3 g (0.05 mole) of amino ketone I and 20.4 g (0.1 mole) of aluminum isopropoxide in 180 ml of isopropyl alcohol was refluxed for 4 h, after which it was cooled to 0° and hydrolyzed with 60 ml of 50% NaOH solution. The organic layer was separated, acidified to pH ∿ 2 with hydrochloric acid, and vacuum evaporated to dryness. The residue was dissolved in water, the solution was saturated with potassium carbonate, and the bases were extracted with ether. The extract was dried with $MgSO_4$ and vacuum distilled to give 4.5 g (48%) of a mixture of amino alcohols III and II with bp 72-78° (0.5 mm) and R_f 0.40 and 0.56 (62% amino alcohol III and 38% amino alcohol II). Crystallization of 5.4 g of the mixture of their hydrochlorides gave 1.1 g of the salt of amino alcohol III with mp 180-182°.

Reduction of 11 g (0.05 mole) of the hydrochloride of amino ketone I with 30.6 g (0.15 mole) of aluminum isopropoxide in 200 ml of isopropyl alcohol gave 4.7 g (50%) of a mixture of cis-amino alcohol III (59%) and its trans isomer II (41%).

E) A 9.3-g sample of amino ketone I was hydrogenated in the presence of 1 g of freshly prepared Raney nickel catalyst in 80 ml of methanol at 20°. The reaction was carried out for 10 h until hydrogen absorption ceased. The catalyst was removed by filtration and washed on the filter with methanol. The methanol was removed by distillation, and the residue was vacuum distilled to give 7.5 g (80%) of a mixture of 51% trans-amino alcohol II and 49% cis-amino alcohol III.

2,2-Dimethyl-4e-phenyl-5e-dimethylaminomethyl-4a-hydroxytetrahydropyran (IV). Anhydrous benzene (150 ml) was added under nitrogen to phenyllithium prepared from 2.8 g (0.4 g-atom) of lithium and 32 g (0.2 mole) of bromobenzene in 180 ml of anhydrous ether, after which 11 g (0.05 mole) of the hydrochloride of amino ketone I was added in small portions with cooling (to −10°) and stirring. The mixture was then refluxed for 2 h, after which it was cooled to 0° and acidified to pH ∿ 2 with dilute (1:1) hydrochloric acid. The organic layer was separated, and the aqueous layer was washed with ether and saturated with potassium carbonate. The base was extracted with ether, and the extract was dried with $MgSO_4$ and filtered. The ether was removed from the filtrate by distillation, and the residue was crystallized to give 7.5 g (57%) of amino alcohol IV with mp 75-76° and R_f 0.56. IR spectrum: 3110 cm^{-1} (OH_{bond}) the integral intensity was $6.35 \cdot 10^4$ $cm^{-2} \cdot mole^{-1} \cdot liter$. Found: C 72.6; 72.5; H 9.5, 9.3; N 5.4 5.5%. $C_{16}H_{25}NO_2$. Calculated C 72.9; H 9.6; N 5.3%. The hydrochloride had mp 210-212°. Found: Cl 11.9, 12.0%. $C_{16}H_{25}NO_2 \cdot HCl$. Calculated: Cl 11.8%.

2,2-Dimethyl-5e-dimethylaminomethyl-4e-acetoxytetrahydropyran (V). Acetyl chloride (6 ml) was added to a solution of 4.7 g of amino alcohol II in 20 ml of benzene, and the mixture was refluxed for 3 h. It was then cooled, and the resulting precipitate was removed by filtration and washed on the filter with ether to give 5.7 g (81%) of the hydrochloride of acetate V with mp 180-182°. Found: Cl 13.5, 13.6%. $C_{12}H_{23}NO_3 \cdot HCl$. Calculated: Cl 13.3%. Base V had bp 84-86° (1 mm) and n_D^{20} 1.4582. IR spectrum: 1240 (C−O) and 1745 cm^{-1} (C = O). Found: C 63.1, 63.2; H 10.3, 10.2; N 6.4%. $C_{12}H_{23}NO_3$. Calculated: C 62.8; H 10.1; N 6.1%.

2,2-Dimethyl-5a-dimethylaminomethyl-4e-acetoxytetrahydropyran (VI). Reaction of 4.7 g of amino alcohol III and 6 ml of acetyl chloride in 20 ml of benzene gave 6.6 g (86%) of the

hydrochloride of VI with mp 166-168°. Base VI had bp 87-88° (1 mm), n_D^{20} 1.4605, and R_f 0.55. IR spectrum: 1240 (C—O) and 1740 cm^{-1} (C=O). Found: N 6.1, 6.3%. $C_{12}H_{23}NO_3$. Calculated: N 6.1%.

2,2-Dimethyl-4e-phenyl-5e-dimethylaminomethyl-4a-acetoxytetrahydropyran (VII). A solution of 6 ml of acetyl chloride in 80 ml of ether was added with cooling (to 0°) to the lithium alkoxide of amino alcohol IV, obtained as described above from 5.5 g of the hydrochloride of amino ketone I, and the mixture was allowed to stand overnight. It was then decomposed with cooling (to 0°) and stirring with dilute (1:1) hydrochloric acid until the solid material dissolved, after which it was worked up as described in the experiment for the preparation of amino alcohol IV to give 3.9 g (51% based on amino ketone I) of crystalline base VII with mp 78-80° and R_f 0.78. IR spectrum: 1240-1275 (C—O) and 1750 cm^{-1} (C=O). Found: C 71.0; 71.1; H 9.0, 9.1; N 4.6, 4.7%. $C_{18}H_{27}NO_3$. Calculated: C 70.8; H 8.9; N 4.6%. The hydrochloride had mp 168-170°. Found: Cl 10.5, 10.4%. $C_{18}H_{27}NO_3 \cdot HCl$. Calculated: Cl 10.4%.

Reaction of 2.6 g of amino alcohol IV and 3 ml of acetyl chloride in 10 ml of benzene gave 2.7 g (88%) of the hydrochloride of VII with mp 168-170°.

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